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Review Article

From the Gothenburg cohort to the Swedish multiple sclerosis registry

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An overview of prevalence and incidence studies performed in Swedish centres is provided, showing improving coverage and methodology, notably the development in Gothenburg of the representative incidence cohort design. A common database for major Swedish centres was established in 1995, implementing the terminology of predictors from the Gothenburg cohort. By 2001, these databases were merged into the web-based national multiple sclerosis (MS) registry, which has had an ever-increasing coverage, although with still moderate data density. The registry now contains records on 13,000 Swedish patients with MS. It has the status of a national quality registry and exerts nation-wide pharmacological surveillance. In addition, it has been, and is being, used in nearly 100 scientific studies, including large epidemiological and genetic projects.

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Introduction

Multiple sclerosis (MS) epidemiology in Sweden has developed considerably during the last 70 years concerning coverage and the choice of parameters (Table 1). The first surveys aimed to obtain the *crude prevalence* of diseases. After a similar survey of thyrotoxicosis, patients with MS were searched for at a national level (1). Using official hospital statistics, medical records for a 10-year period were retrieved. In addition, a questionnaire was answered by a majority of patients. With these means, a national prevalence was obtained, of which 55 cases were looked up in Gothenburg, indicating a crude local prevalence of 23/100,000. The low rate reported in 1942 is explained by the confinement to hospitalized cases and the uneven deployment of neurology at that time in Sweden. Thirty per cent of collected records were discarded by the author for insufficient evidence, and some centres stuck to the archaic definition of Charcot's triad.

The first description, based on a large patient material, of the now classical dichotomy of MS cases in patients with remitting and a progressive course was provided by Professor Müller, in his thesis at the Karolinska Hospital (1949). However, the population basis of his large cohort was not well defined (2).

The Gothenburg cohort

An important improvement in epidemiological methodology was *incidence cohort* studies, often following the exploration of the prevalence of the population base. An incidence cohort includes new cases at onset in a population with both geographically and temporally restricted inclusion (3–5). This type of cohort provides optimal representativeness (as long as a number of other preconditions are fulfilled). An incidence cohort with onset from 1950–1964 in residents of Gothenburg on the western coast of Sweden was designed by Tore Broman at the University of Gothenburg after early contacts with Leonard Kurland at the Mayo Clinic, Rochester (6, 7). A series of studies from an MS register in Gothenburg were reported (1969–2012) with emphasis on this incidence cohort. Here, circumstances were in favour of a high degree of representativeness: There was

Table 1 Prevalence and incidence studies of MS in Sweden

Reference	Study cohort	Prevalence *n*/10(5)/year	Incidence *n*/10(5)/year
Sällström (1)	Hospital series in Sweden	21	NA
Broman et al. (3)	Prevalence and ncidence cohort – Gothenburg	NA	5.3
Svenningsson et al. (13)	Prevalence and incidence cohort – Gothenburg	91	4.0
Sundström et al. (18)	Prevalence and incidence cohort – Västerbotten	164	5.2
Boström et al. (23)	Prevalence and incidence cohort – Värmland	170	6.4
Ahlgren et al. (24)	Swedish MS registry and official hospital statistics	189	NA

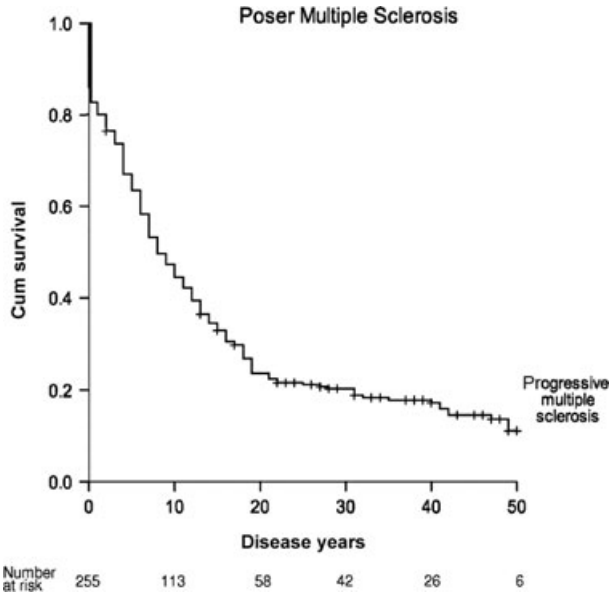

Figure 1. The survival curve shows the decreasing probability of remaining in a non-progressive course during the follow-up in patients with multiple sclerosis (MS) according to the Poser criteria. The probability was calculated using the Kaplan–Meier method. The steps on the curve indicate the point in time when one or several individuals reached the endpoint progressive course. The crosses on the lines indicate the point in time for censored observations. In this survival curve, all primary progressive MS cases have their onset at time 0. The table below the graph shows the number of patients still at risk for progression during the disease year indicated, for example, those who had not yet reached the endpoint or been censored. The inserted graph was reproduced with permission from Oxford Journals (12).

a strong tradition for GPs to refer patients with MS or suspected neurological symptoms to the Gothenburg University Neurology Department, which was the only neurological unit in the region until 1970s. For prevalence and incidence, we always used onset-adjusted data (Onset Adjusted Prevalence (8)), with a record starting from onset (not from diagnosis), and 'spider' epidemiology with intense case ascertainment to catch all cases with onset during the incidence period, continuing during and after the end of the incidence period. Therefore, some patients had an initial retrospective course, but the follow-up was longitudinal (9–12). The annual incidence was 4.2–4.3/100,000 during the incidence period 1950–1964, slightly lower during 1974–1988, particularly at the end of the second period when ascertainment was incomplete, with a higher proportion of possible cases (13).

Several findings emanated from this MS registry. It provided the first cohort to report association between infectious mononucleosis and MS (14). The incidence cohort design was essential for subsequent studies on the relationship with the HLA type (15) and the interaction with pregnancy (16). A set of robust markers of the individual severity of the course was based on demographic and clinical characteristics of the early course in the incidence cohort. These markers, or 'predictors', included afferent or efferent symptoms, mono- or multifocal symptomatology and remission (or not) from the first attack (17). After the difficulties of implementing data from classical MS cohorts to new patients seen at onset were appreciated (patients with clinically isolated syndrome (CIS) only had been excluded from the classical natural history cohorts), the predictors were essentially confirmed in materials including CIS and allowing possible MS as an outcome. Predictors were also identified at a point in time 5 years after onset (11). A long-term follow-up of the representative incidence cohort using Kaplan–Meier analysis showed that 14% of cases were non-progressive with relapse frequency tapering towards zero after 50 years of follow-up (12) (Fig. 1). These patients had a normal social function, EDSS 0-3.5 with deficits attributable to previous relapses, the last of which occurred 18 years after onset (median), and only minor neuropsychiatric deficits. Ten of 11 examined with cerebral magnetic resonance imaging (MRI) had chronically appearing periventricular lesions characteristic of MS (Fig. 2). Thus, a benign course of 50 years after onset, at the age of population life expectancy, is a clinical reality and not uncommon, although extrapolation of hazard curves may suggest that the individual risk of progression will never subside completely. This study lends a further dimension to the concept of benign MS, suggesting that our longitudinal sift-

ing for neurologically benign (non-progressive) cases also selected for patients with little neuropsychological deficit.

A markedly higher incidence was reported from Umeå in Västerbotten county in northern Sweden (18). The authors performed a qualified incidence study prepared for by a prevalence study in the same population. They used a stringent retrieval procedure combining official inpatient and (partially) outpatient databases with six additional data sources. Crude prevalence for 1997 was 154/100,000, with an increase noted since 1990 attributed to a decreased mortality. The 1988–1997 annual incidence was 5.2/100,000, higher than that of Gothenburg, but within the prevalence distribution reported by other Scandinavian centres. The difference between Umeå and Gothenburg might depend on improved case ascertainment, impact of improved diagnostic methods, despite unchanged diagnostic criteria (19), and possibly to a north–south prevalence gradient. It remains to be determined whether the incidence shows a corresponding surge.

The Swedish MS registry

The European Database for Multiple Sclerosis (EDMUS), originally derived from MS epidemiological studies in Lyon, France, since 1976 (20), had reached international dissemination. The implementation of this database in Scandinavia was discussed at the Oslo Think Tank before the meeting in September 1994. At the same time, the first common software, Interactive Database for Multiple Sclerosis (IDMS), for several local Swedish databases was developed at the Huddinge (now integrated into the Karolinska) University Hospital in Stockholm 1995. Set-ups of EDMUS and IDMS were demonstrated in parallel at the 14th ECTRIMS meeting in Stockholm 1998.

What was registered in the IDMS?

Basic demographic data, clinical data on visits, type of course (including an obligatory statement whether transition to a progressive course occurred), relapses and treatment were registered in the IDMS. Notably, definitions on predictive features of the onset attack and relapses were adapted from those demonstrated in the Gothenburg Incidence Cohort described previously. These markers, under certain preconditions 'predictors', from the incidence cohort were included as four concise yes–no queries in the IDMS user interface (*Monosymptomatic optic neuritis? Pure afferent symptoms other than optic neuritis? Complete remission after 1 year? Monofocal symptoms*?)

In 2001, it was decided to combine several Swedish IDMS databases, starting with the university hospitals, into the web-based national Swedish MS (SMS) registry. This registry has since been improved in several respects. Visits from the members and associates of the steering committee to local centres helped to successively involve all Swedish neurology clinics and increase coverage (Figs 3–4). The registry was accredited and remunerated as a Swedish national quality control register. Several associated registries increased its usefulness. Thus, the occurrence and titres of neutralizing antibodies against interferon-beta were analysed in a central laboratory in Stockholm and recorded in the registry since 2007. A central function for the registry was to monitor the extent of immunomodulating treatment in the different stages of the disease at the national level and to describe that in the yearly

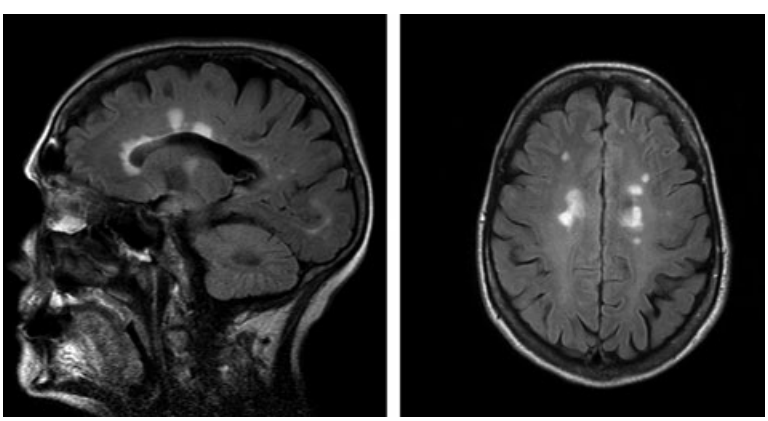

Figure 2a and b. Chronically appearing callosomarginal plaques in MRI (sagittal and transversal FLAIR images) in a woman with non-progressive multiple sclerosis (MS), EDSS = 0 and normal cognitive function according to neuropsychological tests 50 years after the onset of MS.

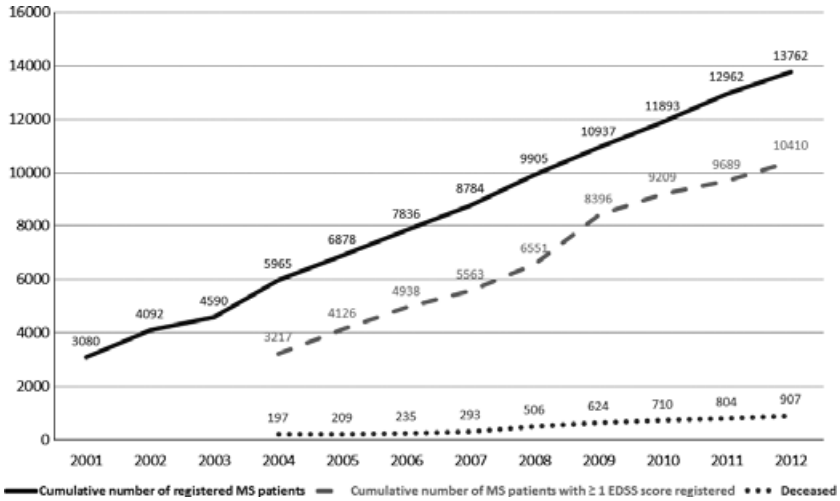

Figure 3. Cumulative number of patients with multiple sclerosis (MS) in the Swedish national MS registry, 2001–2012 (www.msreg.net).

reports (Fig. 5). After the first yearly reports revealed the (inappropriate) use of disease-modifying therapy in many progressive patients, the subsequent yearly reports showed a tendency towards less treatment in progressive stages and reciprocally increased therapeutic activity in the relapsing–remitting stages. This indicated stricter indications, probably facilitated by these reports. Special templates were designed for the recording of the novel immunomodulating drugs approved (natalizumab, fingolimod), prompting users to regularly monitor effect variables and adverse events, with the adverse event module linked to the Swedish Medical Products Agency. The registry was also linked to the national population registry. Data are imported from the Swedish Cause-of-Death Registry for specific projects. From 2009, the user interface included a graphical description of the individual course, a feature much appreciated by the neurologists. Quality-of-life scales and templates evaluating working capacity were implemented. In 2010, following several revisions of the international diagnostic criteria for MS (21, 22), the term 'possible' MS was scrapped. Instructions and schedules for follow-up of all new drugs, toxicology tests and adverse event registration were included and directly linked to the Swedish Medical Products Agency.

Some setbacks occurred. In 2009, the MS diagnosis was inadvertently revealed for some patients with CIS when a study questionnaire was distrib-

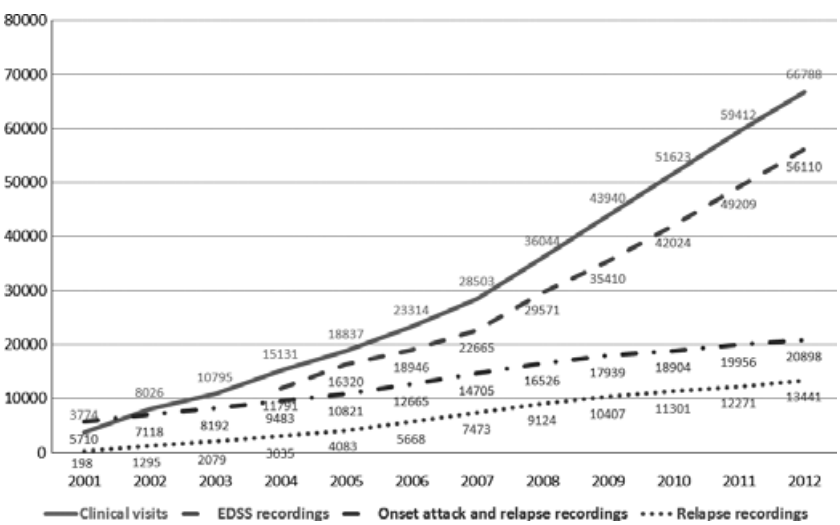

Figure 4. Cumulative number of registered clinical visits, EDSS, onset attacks and relapses in the Swedish national multiple sclerosis registry, 2001–2012 (www.msreg.net).

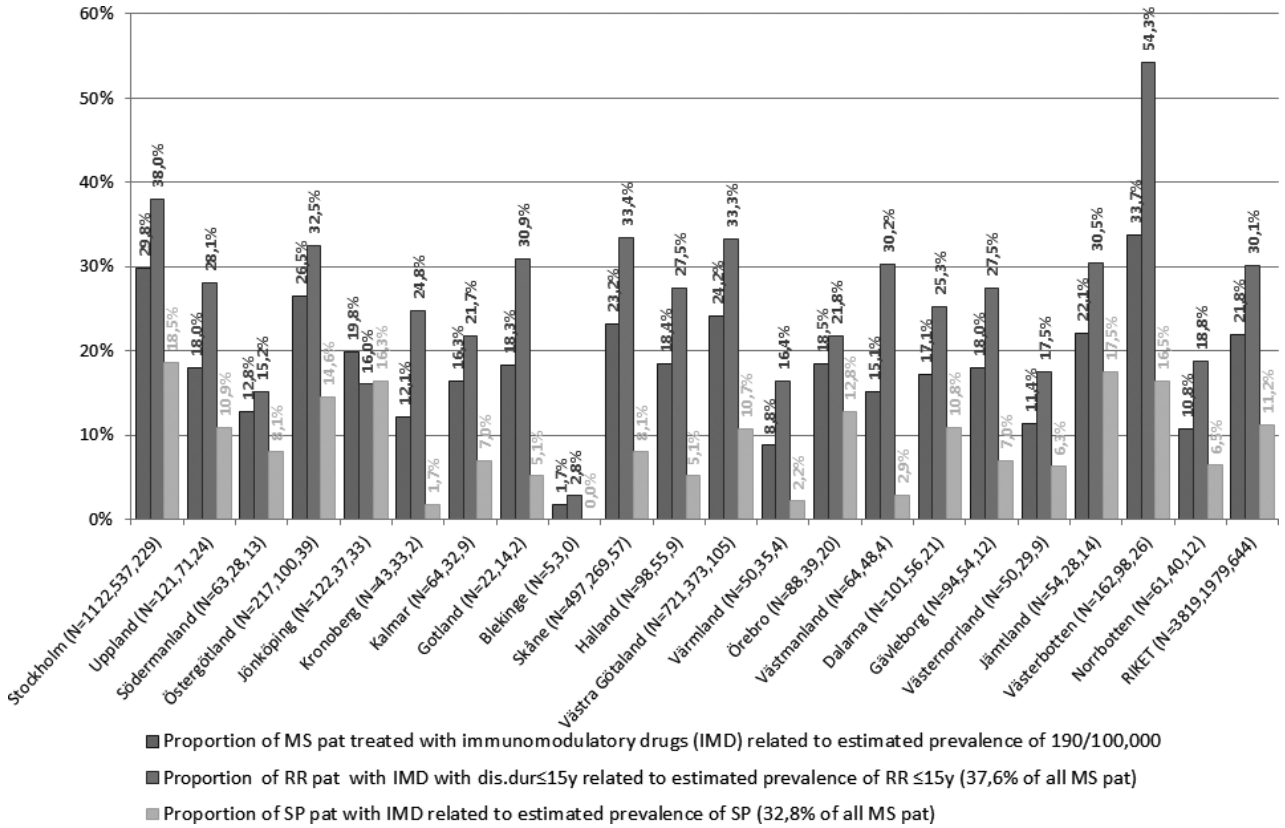

Figure 5. Percentage of patients with multiple sclerosis (MS) on disease-modifying therapy recorded in SMSregistry related to expected number of patients with MS based on estimated total prevalence of 190/100,000 (RR course, SP course and total), all Swedish counties (www.msreg.net).

uted. The requirement for written consent was revised. In 2010, the registry was subjected to control from the Swedish Data Inspection Board and received recommendations for improvement on several aspects, leading to the following modifications: (i) A new central organization was established, with the Chief of Neurology at the Karolinska Hospital as chairman. (ii) The log-in procedure was improved. The system currently requires a two-step authorization: a log-in with personal password followed by a one-time verification code, delivered by phone Short Message Service (SMS) or electronic mail (e-mail). (iii) As the registry was only allowed to be used for quality recording purposes and research, and not for clinical use, individual patients' data can be visualized only locally at each reporting unit (in both structured text form and in a graphical overview). The consent procedure was re-written. Perhaps, surprisingly, only oral consent documented in the medical record (implicating that the patient was informed of the diagnosis), not written consent, was now required.

The number of items recorded has increased considerably, from the addition of questionnaires and quality-of-life data, and patients' on-line self-recordings. Recently, a relative decline in the frequency of relapse ascertainment was noticed. This trend led to a decision of the steering committee to specify core data in the registry.

The Swedish MS registry for research

A large number of applications and projects were based on the SMS registry. Twenty-nine projects have been approved by its Internal Research Committee, and 85 publications appeared during 2011 (n = 21), 2010 (n = 28), 2009 (n = 8), 2008 (n = 8), 2007 (n = 6) and 2003–2006 (n = 14). The difference between numbers of approved and published projects results from local projects not required to obtain central research committee approval and from central projects resulting in multiple publications. An updated report is posted at www.msreg.net, and we here only mention a few comprehensive studies. The 'virtual placebo' studies strive to evaluate the long-term effect of ViP using the predictors to partially justify for difference between treated patients and historical controls. The 'Epidemiological Investi-

gation of Risk Factors for MS (EIMS)' is a case–control study, in which newly diagnosed patients and matched controls are asked to give a blood sample and answer a questionnaire. Data from more than 1600 cases and 3200 controls are currently collected. The intention is to continue with the data collection over several years to analyse how genes and environment interact. The aim of the 'Genes and Environment in Multiple Sclerosis (GEMS)' study is to investigate how genes and environmental factors are interacting in the development of MS. The Immunomodulation and Multiple Sclerosis Epidemiology 'IMSE'studies are two clinical phase 4 studies with the aim to monitor and analyse the importance of different demographic and clinical characteristics for the effect of two immunomodulatory drugs for MS on the background of the natural course. Within the IMSE-I study, the drug Tysabri (natalizumab) is investigated, and within IMSE-II, Gilenya (fingolimod). Long-term follow-up of the patients is carried out via the MS registry to detect any new unknown adverse events beyond the years of earlier controlled clinical trials. A further purpose is to map individual factors (e.g. genes and/or soluble factors in blood) that might be of importance for the generation of active and severe MS as opposed to the benign form of MS. The registry has been ideal for updated prevalence studies. The prevalence was found to be 170/10,000 in the western county of Värmland (23), and the annual incidence was 6.4 –6.5/100,000 in this region. As was previously noted in the Västerbotten study, the official statistics have a good coverage in Sweden. By combining the MS registry with the official statistics, the crude prevalence was estimated at 190/100000, with a moderate south–north gradient (1.5% per degree) (24). The prevalence of Iranian immigrants was as high as in native Swedes (25).

In addition to providing a basis for the scientific production and for open quality comparisons, we believe that the national MS registry will promote a more open, matter-of-fact attitude to MS in our patients, relatives, students and the general population. The registration in the MS registry is optional but accepted by almost all patients with this diagnosis, while as much as 35% of people newly diagnosed with MS in the UK were still not informed of the diagnosis (National Audit Office, Report by the Controller and Auditor General, Department of Health, December 16, 2011). The very convenient graphic interface is useful (with local constraints described earlier) for individual information – a feature that certainly facilitates accept by clinical neurologists. If the present trend (Figs 3–5) continues, it is realistic to expect next to complete coverage of Swedish patients with MS. Still, data from the registry revealed surprisingly large local differences in disease duration between counties.

In 2011, the MS registry was incorporated into a national Swedish Neurology Registry, combining with a number of other diagnosis-based registries, including Parkinson's disease, myasthenia gravis (MG), Guillain–Barré syndrome (GBS), narcolepsy and others. The number of registered patients by 2011 in the Swedish Neurology Registry was as follows: MS, 12,973; Guillain–Barré syndrome, 17; myasthenia gravis, 490.

In conclusion, local MS registries obtained increased coverage largely substituted by or absorbed into the Swedish national MS registry, which is now accredited as a national quality control register, promoting uniform routines in MS therapy and a basis for several qualified epidemiological, genetic research projects. An important asset has been the evolution of the registries, with a conservative attitude towards items recorded and definitions originally used in the Gothenburg cohort.

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Conflicts of interest

The author has no conflicts of interest to declare.

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